

Recent Advancements in the Synthesis and Pharmacological Evaluation of Substituted 1, 3, 4-Thiadiazole Derivatives

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Abstract: Chemical properties of 1,3,4-thiadiazole have been reviewed in the last few years. However, the usefulness of 1,3,4-thiadiazole as a privileged system in medicinal chemistry has prompted the advances on the therapeutic potential of this system. This review provides a brief summary of the medicinal chemistry of 1,3,4-thiadiazole system and highlights some examples of 1,3,4-thiadiazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 1,3,4-thiadiazole is presented in sections by generalized synthetic methods.

Keywords: 1, 3, 4-Thiadiazole; Rearrangement; Ring opening; Substitution Reaction; Therapeutic efficacy.

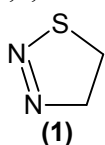
Introduction

Over the past decade, drug resistance has become a growing problem in the treatment of infectious disease caused by bacteria, fungi and viruses. In particular, resistance of bacterial pathogens to current antibiotic has emerged as a measure health problem. This is especially true in case of infectious diseases such as pneumonia, meningitis and tuberculosis, which would once have been easily treated with antibiotics, is no longer so readily treated. At present, all widely used antibiotic, including some of the agent such as streptogramins and new generation flouroquinolones are subjected to bacterial resistance. The search for new antimicrobial agent is one of the most challenging tasks to the medicinal chemist.

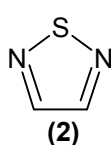
A recent literature survey revealed that the 1, 3, 4-thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities.

The Development of 1, 3, 4-Thiadiazole Chemistry is linked to the discovery of Phenylhydrazines and hydrazine in the late nineteenth century. The first 1, 3, 4-Thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh.

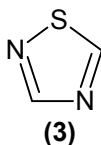
There are several isomers of thiadiazole, that is 1,2,3 Thiadiazole (1), 1,2,5 Thiadiazole (2), 1,2,4 Thiadiazole (3) and 1,3,4 Thiadiazole (4).



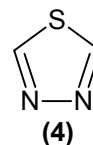
1,2,3 Thiadiazole



1,2,5 Thiadiazole



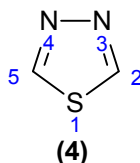
1,2,4 Thiadiazole



1,3,4 Thiadiazole

1,3,4 Thiadiazole is the isomer of thiadiazole series. A glance at the standard reference works shows that more studies have been carried out on the 1,3,4 Thiadiazole than all the other isomers combined. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents.

The ending *-azole* designates a five membered ring system with two or more heteroatoms, one of which is Nitrogen. The ending *-ole* is used for other five membered heterocyclic ring without Nitrogen. The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence the numbering of 1, 3, 4 Thiadiazole (4) is done in following manner. This designates that one sulphur group is present in the ring.



1, 3, 4 Thiadiazole: -

During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial¹⁻³, antituberculosis⁴, anti-inflammatory⁵⁻⁷, anticonvulsants^{8,9}, antihypertensive^{10,11}, antioxidant¹², anticancer^{13,14,15} and antifungal¹⁶ activity.

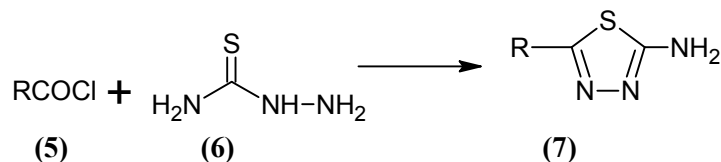
Recent Strategies in the Synthesis of 1, 3, 4-thiadiazoles: -

Recent strategies on the synthesis of 1, 3, 4 Thiadiazole derivatives can be summarized in to following points:-

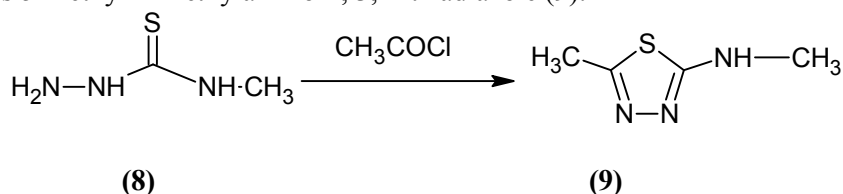
(a) From Thiosemicarbazides:-

Many synthesis of the 1, 3, 4 Thiadiazole proceed from thiosemicarbazide or substituted thiosemicarbazide.

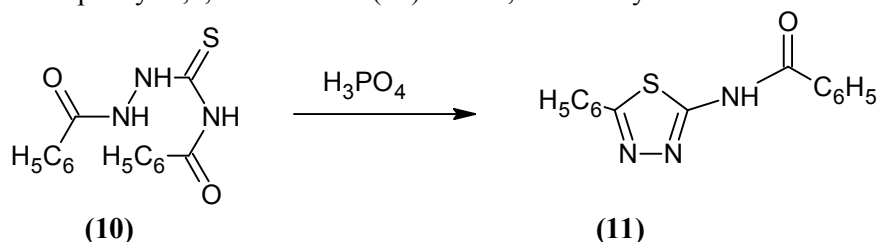
Method 1. Frund and Meinecke¹⁷ have shown that thiosemicarbazide (6) cyclizes directly to 2-amino-5-methyl-1, 3, 4-thiadiazole (7) with acetyl chloride (5). This simple route to 2-amino 5-substituted-1, 3, 4-thiadiazole seems to be quite general. In the example shown R may be methyl¹⁷, norhydnoctyl¹⁸, benzyl¹⁹, cyclopropyl²⁰ and many others.



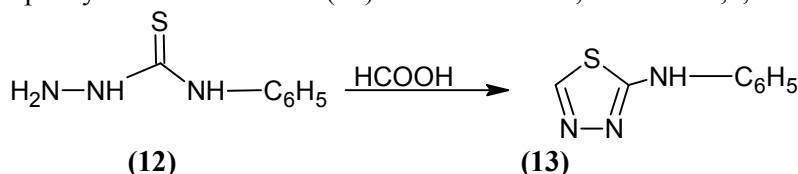
Pulvermacher²¹ had earlier shown that acetyl chloride (5) could bring about the cyclization of alkyl – or aryl-substituted thiosemicarbazide. For example, the action of acetyl chloride on 4-methylthiosemicarbazide (8) produces 5-methyl-2-methylamino-1, 3, 4-thiadiazole (9).



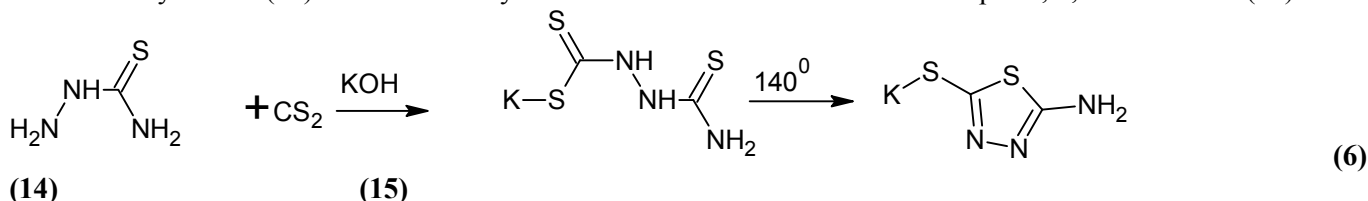
Method 2. Hoggarth²² has prepared a number of 2-amino-5-aryl-1,3,4-thiadiazole using phosphoric acid as the dehydrating agents. An example of smooth cyclization in high yield by phosphoric acid is the formation of 2-benzamido-5-phenyl-1,3,4-thiadiazole (11) from 1,4-dibenzoylthiosemicarbazide (10).



Method 3. Pulvermacher²¹ observed that formic acid could cyclize the alkanoyl halides by acylation. He found that by heating 4-phenylthiosemicarbazide (12) with formic acid, 2-anilino-1,3,4-thiadiazole (13) was formed.

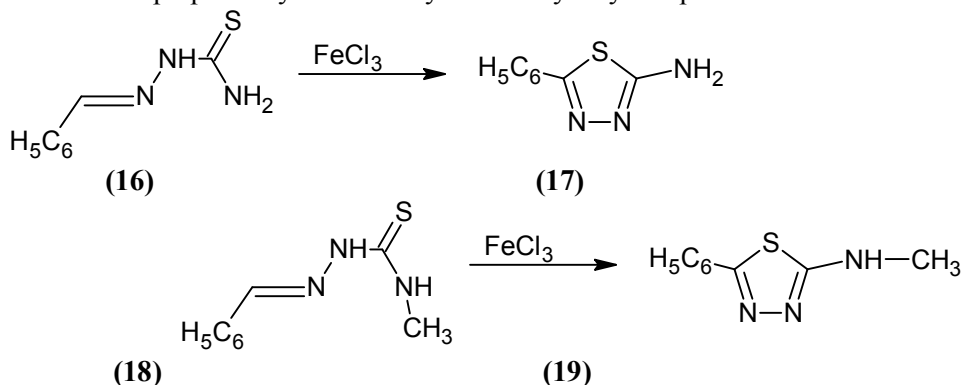


Method 4. A useful preparative method for 2-amino-5-mercapto-1, 3, 4-thiadiazole (6) was developed by Guha²³. When thiosemicarbazide is treated with carbon disulphide and potassium hydroxide, the potassium salt of thiosemicarbazide-4-dithiocarboxylic acid (14) is formed. Heating this potassium salt of thiosemicarbazide-4-dithiocarboxylic acid (14) to 140° causes cyclization to the salt of 2-amino-5-mercapto-1, 3, 4-thiadiazole (15).



Guha²³ also showed that in certain instances neutral carbon disulphide react directly with thiosemicarbazide to form aminomercaptothiadiazoles. A modification of the carbon disulphide-thiosemicarbazide procedure which results in higher yield of 2-amino-5-mercapto-1, 3, 4-thiadiazole is carried out in dimethylformamide at 80°, the yield is over 90%.

Method 5. Young and Eyre²⁴ reported that benzalthiosemicarbazones (16) could be oxidatively cyclize to form 2-amino-5-phenyl-1, 3, 4-thiadiazole (17) by ferric chloride. A large number of 5-substituted 2-amino-1, 3, 4-thiadiazole have been prepared by De and Roy-Choudury²⁵ by this procedure.

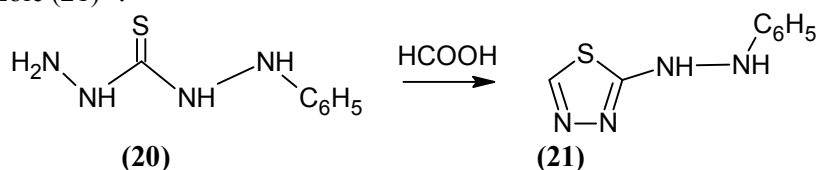


Holmberg²⁶ found that a number of aldose thiosemicarbazones could be converted to thiadiazole derivatives by Young and Eyre method.

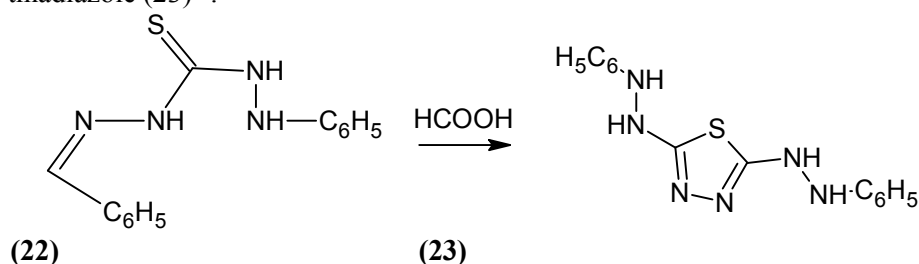
(b) From Thiocarbazides:-

There are two method by which 1, 3, 4-thiadiazole can be prepared from thiocarbazides.

Method 1. If 1-phenylthiocarbazine (20) is heated with formic acid, it is converted to 2-phenylhydrazino-1, 3, 4-thiadiazole (21)²⁷.



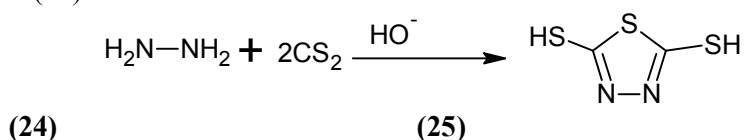
Method 2. This method is related to the oxidation of 1-phenylbenzalthiocarbazon (22) to 2-phenyl-5-phenyl hydrazino-1, 3, 4-thiadiazole (23)²⁸.



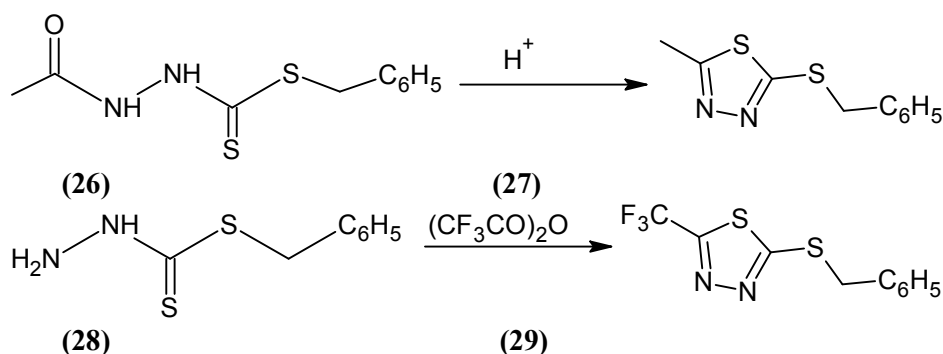
(c) From Dithiocarbazates:-

Following methods have been reported for the preparation of 1, 3, 4-thiadiazole from dithiocarbazates.

Method 1. Another route to 1, 3, 4-thiadiazole is via substituted dithiocarbazic acid and their esters. A reaction which belongs in this group is the formation of 2,5-dimercapto-1, 3, 4-thiadiazole (25) by action of carbon disulphide on hydrazine (24) in basic medium^{29,30}.

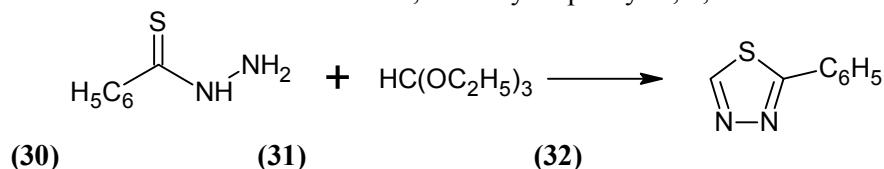


Method 2. When 3-acyldithiocarbazic esters (26, 28) are treated with acids, they cyclize to form substituted thiadiazoles (27, 29)^{31, 32}. This is a quite general reaction. Both benzyl and methyl 3-acyldithiocarbazates have been employed.



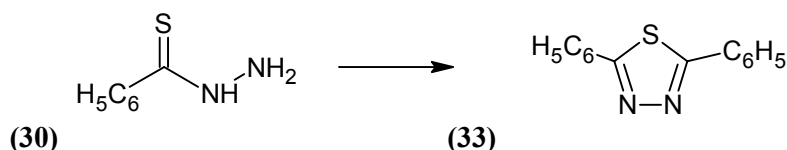
(d) From Thioacylhydrazines:-

Thioacylhydrazines may often serve as starting materials for the preparation of 1, 3, 4-thiadiazole. If thiobenzoylhydrazine (30) is heated with ethyl orthoformate (31), 2-phenyl-1, 3, 4-thiadiazole (32) is formed.³³ If ethyl orthoacetate is substituted for the orthoformate, 2-methyl-5-phenyl-1, 3, 4-thiadiazole is obtained.³⁴



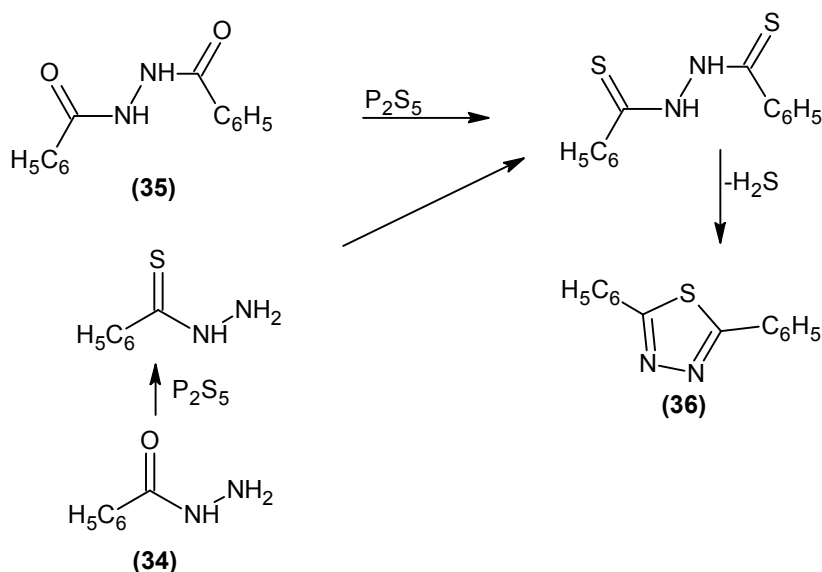
Thiobenzhydrazide is smoothly converted to 2-phenyl-1, 3, 4-thiadiazole by the action of formic acid.²⁶

Thiobenzhydrazide is reported by Holmberg³⁵ to form 2, 5-diphenyl-1,3,4-thiadiazole (33) in small amount when warmed in benzene.

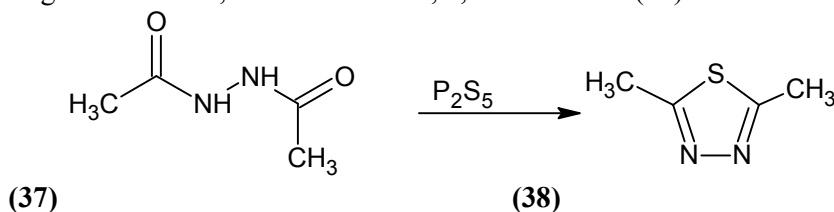


(e) From Acylhydrazines:-

Stolle obtained 2, 5-diphenylthiadiazole (36) by a variety of methods. He found that benzoylhydrazine (34)³⁶ or N, N'-dibenzoylhydrazines (35)³⁷ react with phosphorus pentasulfide to form 2, 5-diphenyl-1, 3, 4-thiadiazole (36).

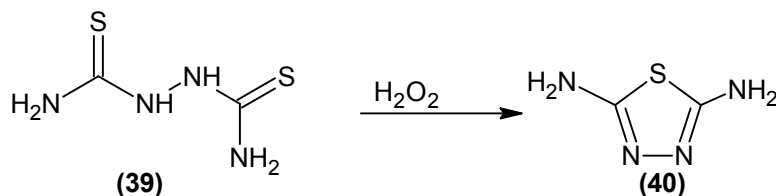


The reaction of N, N'-diacylhydrazine (37) with phosphorus pentasulfide was used by Stolle and his students for the preparation of a large number of 2, 5-disubstituted 1, 3, 4-thiadiazole (38).^{38, 39}



(f) From Bithioureas:- Bithiourea and substituted bithioureae have been converted to 1, 3, 4-thiadiazole by several methods.

Method 1: Bithiourea (39), when treated with 3% hydrogen peroxide is cyclized to 2, 5-diamino-1, 3, 4-Thiadiazole (40).⁴⁰

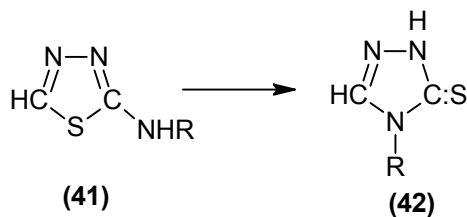


Method 2: Acetic anhydride acts on bithiourea to form a diacetyl derivative of 2, 5-diamino-1, 3, 4-Thiadiazole. The acetyl group is easily removed by hydrolysis to give the parent thiadiazole.⁴¹

Reactivity of the 1, 3, 4-thiadiazoles:

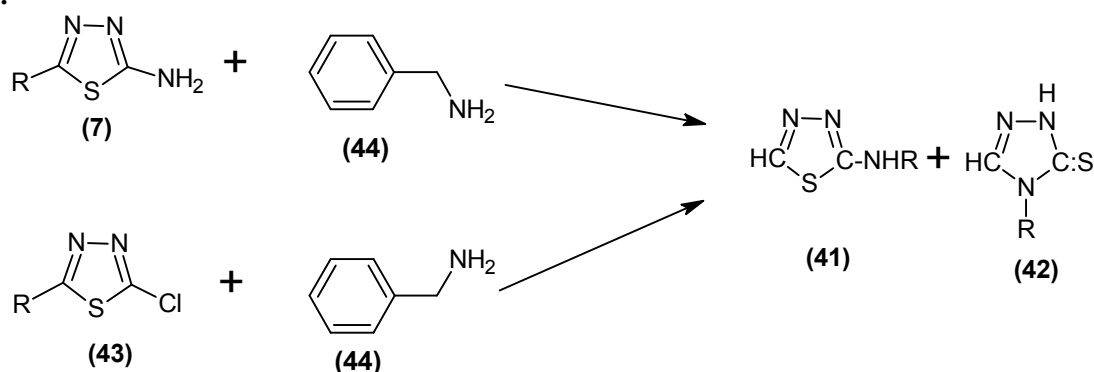
(A) Rearrangements and Ring Opening Reaction :-

The 1, 3, 4-thiadiazole ring is rather susceptible to attack by strong nucleophile. Thus the parent compound is stable to acids but is readily cleaved by bases⁴². 2-Amino- and 2-hydrazino-1, 3, 4-thiadiazole can be rearranged to 1, 2, 4-triazoline-3(2)-thiones. Goerdeler and Galinke⁴³ showed that 2-amino- and 2-methylamino-1, 3, 4-thiadiazole (41, R=H and CH_3) are rearranged by methylamine in methanol at 150° to the isomeric triazolinethiones (42).

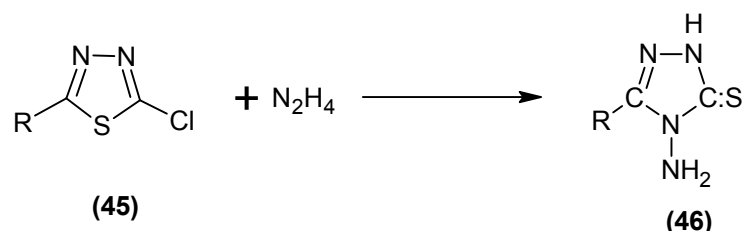


2-Amino 1,3,4-thiadiazole (7, R = H), when refluxed with benzyl amine in xylene, gave a mixture of about equal amount of 2-benzylamino-1,3,4-thiadiazole (41, R = CH_2Ph) and 4-benzyl-1,2,4-triazolin-3(2)-thione (42, R =

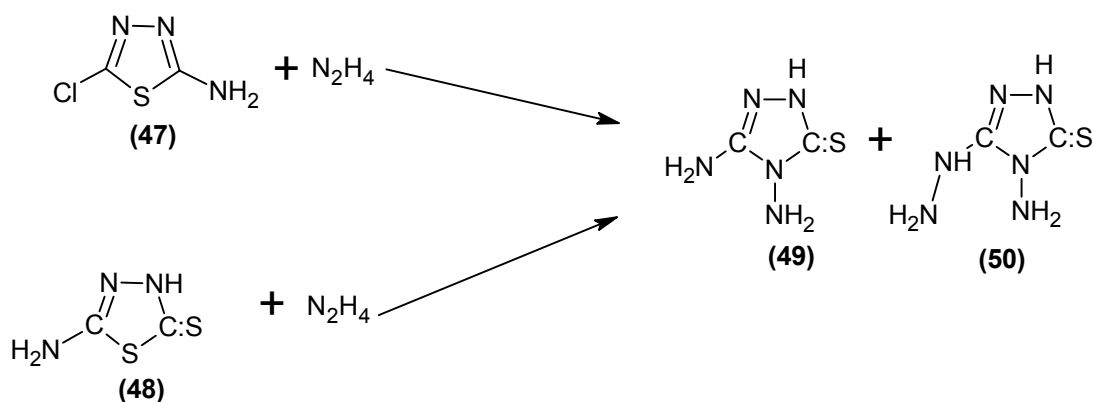
CH₂Ph). The same two compounds were formed in the reaction between 2-chloro-1, 3, 4-thiadiazole and benzyl amine (43).⁴⁴



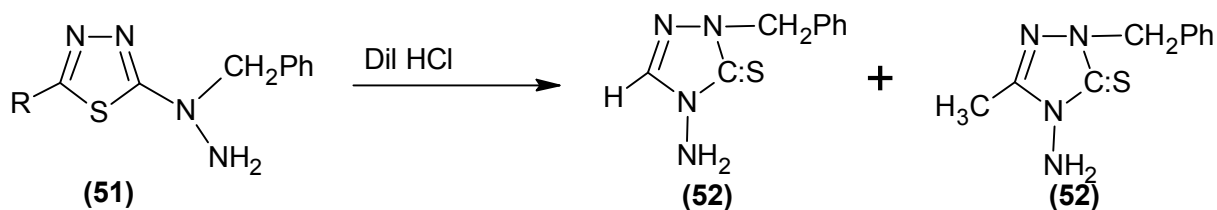
Similarly, 2-alkyl-5-chloro-1, 3, 4-thiadiazole (45) reacted with a large excess of hydrazine hydrate on heating to give 4-amino-1,2,4-triazolin-5(1)-thione (46).



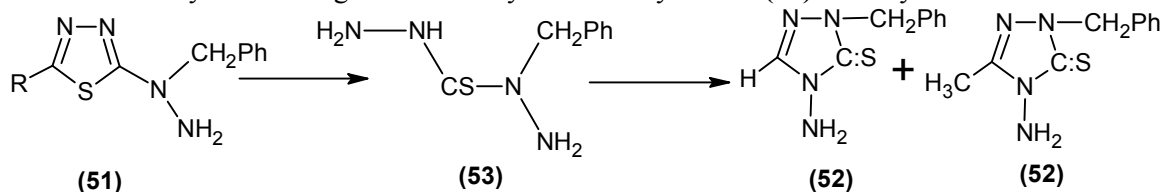
Under the same conditions, 2-amino-5-chloro-1,3,4-thiadiazole (47) and 2-amino-1,3,4-thiadiazolin-5(4)-thione (48) gave a mixture of 3,4-diamino-1,2,4-triazolin-5(1)-thione (49) and 3-hydrazino-4-amino-1,2,4-triazolin-5(1)-thione (50). 2,5-Dichloro- and “2,5-dimercapto-1,3,4-thiadiazole” gave only (50).⁴⁵



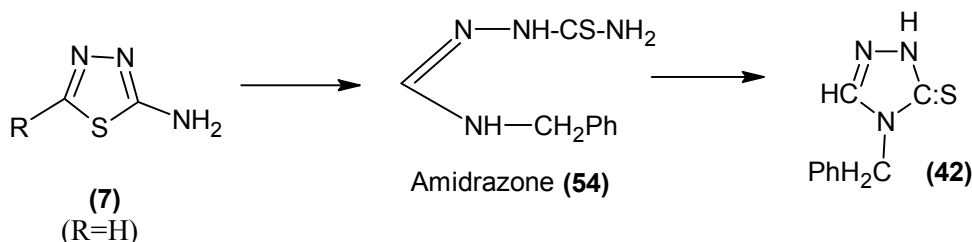
Similar rearrangements can be affected by acids. When 1-benzyl-1-(1, 3, 4-thiadiazole-2-yl) hydrazine (51) was refluxed with dilute hydrochloric acid, the triazolinethion (52, R=H) was formed in quantitative yield. When the reaction was performed in the presence of some acetic acid, a mixture of (52) (R=H) and (52) (R=CH₃) was formed.⁴⁶



In this acid catalyzed rearrangement 2-benzylthiocarbohydrazide (**53**) is likely an intermediate.



The rearrangement of (**7**) by benzyl amine probably proceeds with ring opening to an amidrazone (**54**) followed by recyclization to (**42**) (R=CH₂Ph).



[B] Substitution Reaction:-

Although the 1,3,4-thiadiazole ring is classed as π -excessive according to Albert⁴⁷, the presence of two nitrogen atoms of pyridine type in the ring leaves the carbon atoms with rather low electron density, and consequently no electrophilic substitution in the unsubstituted 1,3,4-thiadiazole ring have been recorded.

Goerdeler et.al.⁴² obtain a bromine adduct of the simple 1, 3, 4-thiadiazole, but it decomposed and lost bromine in the air. Nitration, even under drastic condition could not be achieved.

Ohta et.al.⁴⁸ subjected 2-phenyl-1, 3, 4-thiadiazole to a mixture of concentrated nitric acid and sulphuric acid at 0° and obtained a mixture of the three isomeric 2-nitrophenyl-1,3,4-thiadiazole in the ratio *p*: *m*: *o* = 2:3:1, but no 2-phenyl-5-nitro-1,3,4-thiadiazole.

A 2-amino group does activate the ring towards electrophilic agents, since Bak et.al.⁴⁹ could prepare 2-amino-5-bromo-1, 3, 4-thiadiazole by bromination of 2-amino-1, 3, 4-thiadiazole in 40% hydrobromic acid. The product was not isolated but was diazotized to give 2, 5-dibromo 1, 3, 4-thiadiazole.

Physical properties of -1, 3, 4-thiadiazoles:

Structure and Aromatic Properties:-

Bak et.al.⁵⁰ recently made a careful analysis of the microwave spectra of 1, 3, 4-thiadiazole and three isotopically substituted species. They could determine the structure of the molecule with an uncertainty of 0.03 Å° in the coordinates of the hydrogen atom and of less than 0.003 Å° in the coordinates of the other atoms.

By an analysis of difference between the measured bond lengths and covalent radii, the author came to the conclusion that the aromatic character, as measured by the π -electron delocalization decreases in the order – 1, 2, 5-thiadiazole > thiophene > 1, 3, 4-thiadiazole > 1, 2, 5-oxadiazole

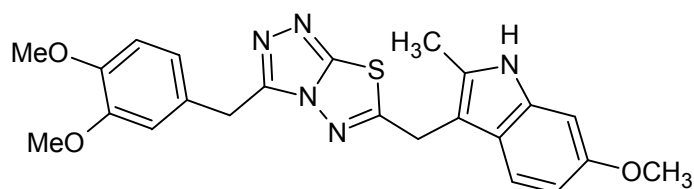
Dipole Moment:-

Bak et.al.⁵¹ measured the dipole moment of 1, 3, 4-thiadiazole in the gas phase by microwave technique and found a value of 3.28±0.03 D. By use of geometry of Bak et.al.⁵⁰ the π -electron distribution of Zahradnik and Koutecky⁵² and the bond moment of Smith⁵³, a dipole moment of 3.0 D can be calculated, directed from the sulphur atom towards the center of the nitrogen-nitrogen bond.

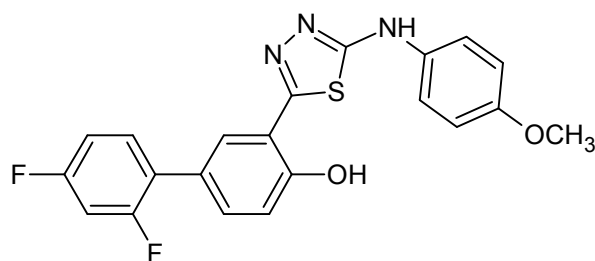
Recent Advancement in the Therapeutic Potential of 1,3,4 Thiadiazole Derivatives:

Analgesic and Anti-inflammatory Activity:-

Vinod Mathew et.al.⁷ have synthesized several 3, 6-disubstituted-1, 2, 4-triazolo[3,4-b]-1,3,4-thiadiazole and their dihydro analogues. They found that anti-inflammatory and analgesic activity screening of the tested compounds 55 showed good anti-inflammatory and analgesic activities.

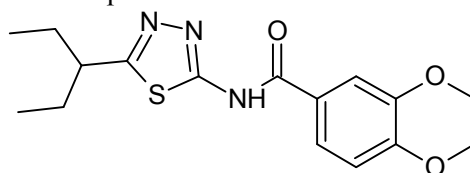
**Fig; Compound 55**

S. Guniz Kucukguzel *et.al.*⁵⁴ have synthesized 2-substituted-1, 3, 4-thiadiazoles. They Found that compound 56 that is 5-(2', 4'-Difluoro-4-hydroxybiphenyl-5-yl)-4-(4-methoxyphenyl)-1, 3, 4-thiadiazole presented similar antinociceptive activity with the standard drug (paw withdrawal latency was 19.21 s compared to that of diflunisal which was 19.14 s, in hot plate test).

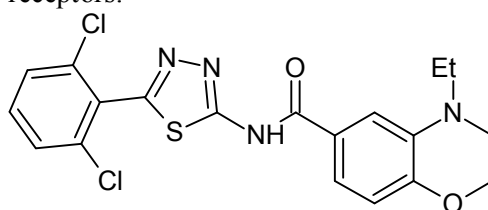
**Fig; Compound 56**

The EP3 receptor is a 7-transmembrane (7-TM) G-protein coupled receptor found in various human tissues. Prostaglandin E2 (PGE2), a primary product of arachidonic acid metabolism by the cyclooxygenase pathway, is the natural ligand attributed to agonism of EP3 as well as other EP receptor subtypes.

Mark A. Hilfiker *et.al.*⁵⁵ have carried out the investigation to identify new selective antagonists, and they found that aminothiadiazoole that is compound 57 was identified from a high throughput screen as having good antagonist activity for human EP3. In addition, compound 1 demonstrated excellent selectivity against other EP subtypes as well as the DP, FP, TP, and IP prostenoid receptors.

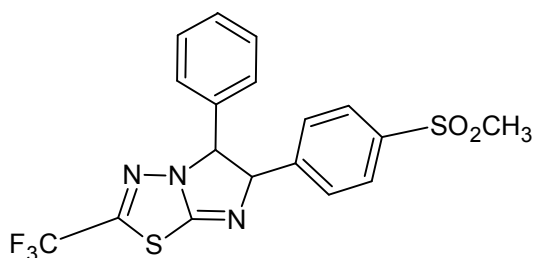
**Fig; Compound 57**

Further, while studying the structure activity relationship of this compound they found that Compound 58 was a potent antagonist against human EP3 receptors.

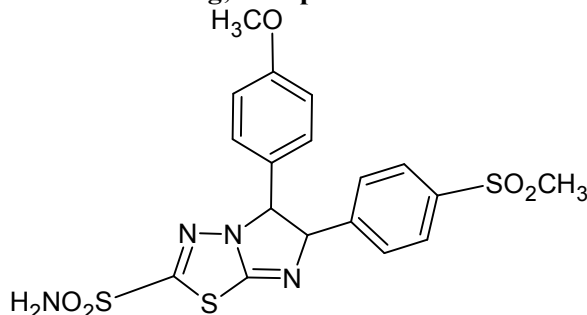
**Fig; Compound 58**

Non-steroidal anti-inflammatory drugs (NSAIDs) continue to be one of the more widely used groups of therapeutic agents, which inhibit COX-1, COX-2, and tromboxane synthase with a varying degree of selectivity. Researchers have recently focused on selective COX-2 inhibitors which are believed to reduce inflammation without influencing normal physiologic functions of COX-1.

Andanappa K. Gadad *et.al.*⁵⁶ have synthesized a series of 2-trifluoromethyl/sulfonamido-5, 6-diarylsusbstituted imidazo [2, 1-b]-1, 3, 4-thiadiazole derivatives. They found that the compounds 59 and 60 tested showed selective inhibitory activity toward COX-2 (80.6–49.4%) over COX-1 (30.6–8.6). These compounds also exhibited significant anti-inflammatory activity (70.09–42.32%), which is comparable to that of celecoxib in the carrageenan-induced rat paw edema method.

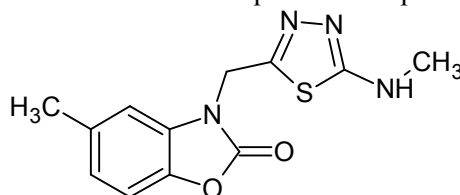


Fig; Compound 59



Fig; Compound 60

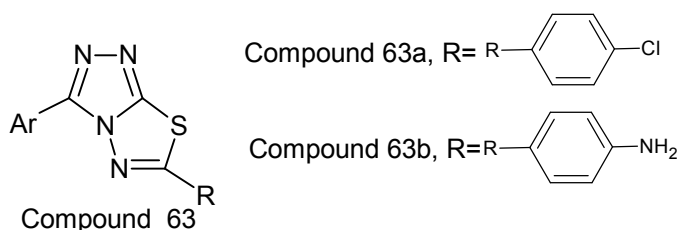
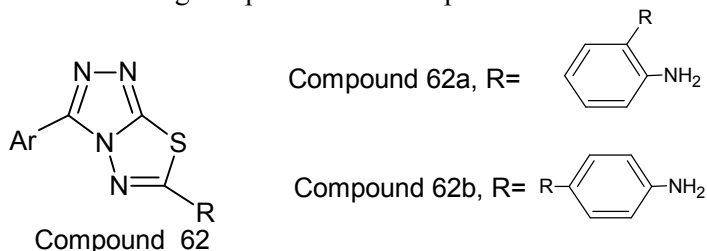
Nesrin Gokhan-Kelekci *et.al.*⁵⁷ have synthesized some 1, 3, 4-thiadiazole derivatives. They found that the analgesic effects of compound 61 were higher than those of both morphine and aspirin.

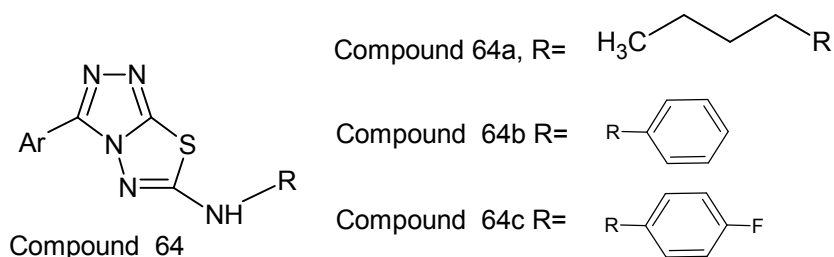


Fig; Compound 61

Currently available non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, flurbiprofen, fenbufen and naproxen exhibit gastric toxicity. Literature survey revealed that modification of the carboxyl function of representative NSAIDs resulted in increased anti-inflammatory activity with reduced ulcerogenic effect^{58, 59}.

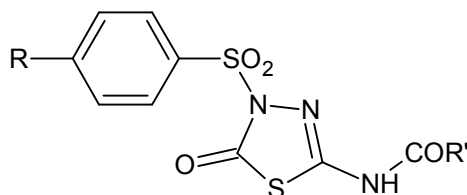
Certain compounds bearing 1, 2, 4-triazole and 1, 3, 4-thiadiazole nuclei possess significant anti-inflammatory activity with reduced GI toxicity. Mohd. Amir *et.al.*⁶⁰ have replaced the carboxylic acid group of 2-(4-isobutylphenyl) propanoic acid and biphenyl-4-yloxy acetic acid by a composite system, which combines both the triazole and the thiadiazole nucleus in a ring to give a compact and planar structure. It was interesting to note that seven cyclized compounds 62a, 62b, 63a, 63b, 64a, 64b and 64c were found to have anti-inflammatory properties comparable to their standard reference drugs ibuprofen and flurbiprofen.





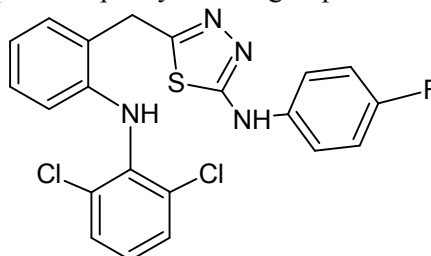
When these compounds were subjected to analgesic activity by tail immersion method in mice, all compounds exhibited moderate to good activity. These compounds were also tested for ulcerogenic activity and lipid peroxidation, and showed superior GI safety profile along with reduction in lipid peroxidation as compared with ibuprofen and flurbiprofen²³.

Silvia Schenone *et al.*⁶¹ have synthesized two series of N-[5-oxo-4-(arylsulfonyl)-4, 5-dihydro-1,3,4-thiadiazol-2-yl]-amides (compound 65) and tested *in vivo* for their analgesic and anti-inflammatory activities. All the new compounds possess good analgesic action in the acetic acid writhing test and some terms of the series showed also fair anti-inflammatory activity in the carrageenan rat paw edema test. Ulcerogenic and irritative action on the gastrointestinal mucosa, in comparison with indomethacin is low.



Fig; Compound 65

Mohd. Amir *et al.*⁶² have synthesized the 1, 3, 4-thiadiazole derivatives of diclofenac and showed anti-inflammatory activity from 79.04% to 82.85%. The maximum activity (82.85%) was shown by thiadiazole derivative that is compound 66 having *p*-fluoro phenyl amino group at second position.



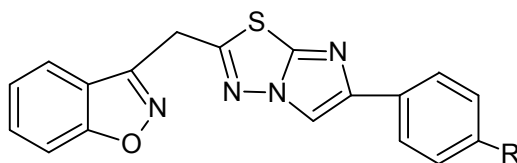
Fig; Compound 66

Antimicrobial and Antiinflammatory Activity:-

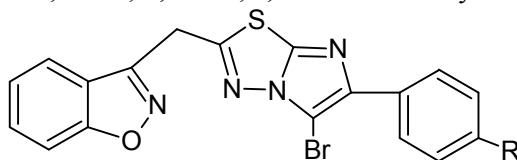
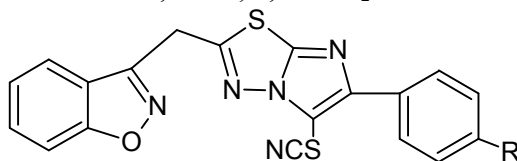
Mohd.Amir *et al.*⁶⁰ have also found that Compound 62b demonstrated about half the activity of ofloxacin against *E. coli*. The other compounds showed moderate to weak antibacterial activity against *S. aureus* and *E. coli*. The synthesized compounds showed weak antifungal activity against *C. albicans*, except for compound 62c that showed half of the activity of the antifungal drug (ketoconazole). Thus the triazolo-thiadiazole derivatives were found having dual functional properties (anti-inflammatory-analgesic and antimicrobial), and represent a promising class of compounds with an interesting pharmacological profile.

Antimicrobial and Antifungal Activity:-

Imtiyaz Ahmed M. Khazi *et al.*⁶³ were synthesized novel methylene bridged benzisoxazolyl imidazo [2, 1-b][1,3,4]-thiadiazoles. The investigation of antibacterial screening revealed that some of the tested compounds showed moderate to good bacterial inhibition. Particularly compounds 67a, 67b, 68a, 68b and 69a have shown very good antibacterial activity. Compound 69a has exhibited highest antibacterial activity. The high activity is attributed to the presence of electron withdrawing chloro- and bromo- functional groups. Antifungal results indicated that compounds 13b, 13c and 69b have shown good activity. Compound 67b showed very good antifungal activity comparable to that of standard.

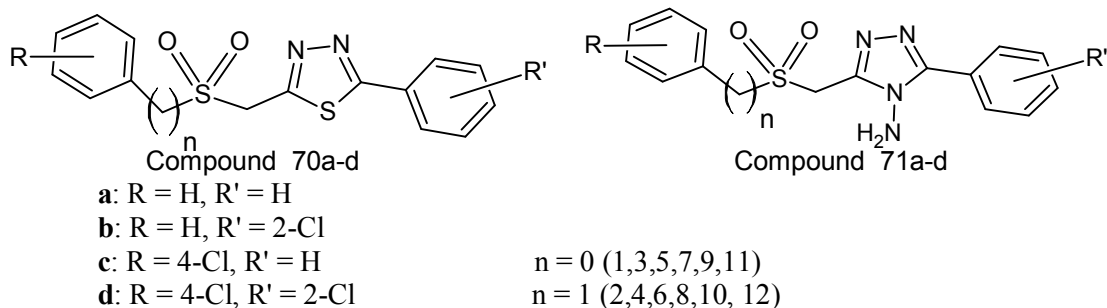
**Fig; Compound 67a-c**

a, R=Cl; b, R=Br; c, R=3-Coumarinyl

**Fig; Compound 68a-b**a, R=Cl; b, R=NO₂**Fig; Compound 69a-b**

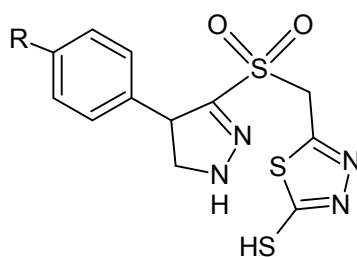
a, R=Cl; b, R=OMe

V. Padmavathi et.al.⁶⁴ have found that 2-(arylmethanesulfonylmethyl)-5-aryl-1, 3, 4 thiadiazoles 70a-d, 3-(arylmethanesulfonylmethyl)-5-aryl-4H-1,2,4-triazol-4-amines 71a-d exhibited high activity (22–39 mm) on both Gram (+ve) and Gram (-ve) bacteria. In fact, compounds 70d and 71d showed pronounced activity (31–39 mm) towards Gram (+ve) bacteria.



Further they found that compounds 2-(4-chlorobenzylsulfonylmethyl)-5-(2-chlorophenyl)-1, 3, 4-thiadiazole (70d) displayed greater activity against spore germination of tested fungi *A. niger*, *F. solani* and *C. lunata*.

V. Padmavathi et.al.⁶⁵ also reported synthesis and biological screening of some novel sulfone-linked bis heterocycles. In which the compounds 72a showed excellent activity against Gram-positive bacteria (inhibitory zone >25 mm), good activity against Gram-negative bacteria (inhibitory zone >20 mm). The compounds (72a-c) showed high inhibitory effect towards tested fungi

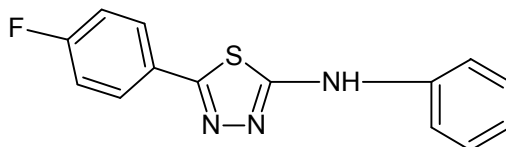


R= a) H, b) Me, c) Cl

Fig; Compound 72a-c

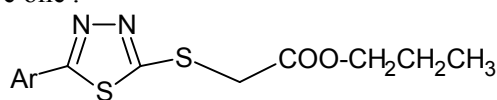
Antituberculosis Activity:-

Sevim Rollas et.al.^{66,67} have found that one of the thiadiazole derivative, namely 2-(4-chlorophenylamino)-5-(4-aminophenyl)-1, 3, 4-thiadiazole, showed 57% inhibition against *Mycobacterium tuberculosis*. Further they found that compound 73 has exhibited the highest inhibitory activity (69% inhibition) against in vitro growing *Mycobacterium tuberculosis*.

**Fig; Compound 73**

This compound while not active enough to be considered as therapeutics, are definitely lead compounds in the search for novel agents to combat resistance.

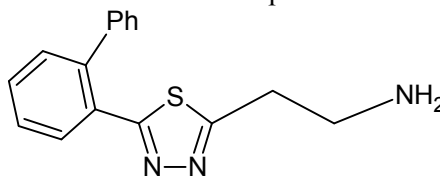
Alireza Foroumadi et.al.⁶⁸ have synthesized two series of 2- and 3-[5-(nitro aryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters and screened for antituberculosis activity against *Mycobacterium tuberculosis* and found that the compound 74 that is Propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio]propionate was the most active one.



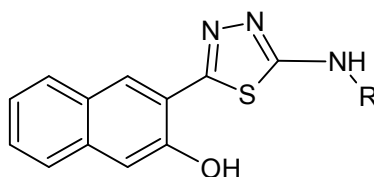
Ar= 5-Nitro-2-thienyl

Fig; Compound 74**Anticonvulsants Activity:-**

Michael R. Stillings et.al.⁶⁹ has described the anticonvulsants properties of a number of substituted 2-hydrazino-1,3,4-Thiadiazole. Further they found that, 2-(aminomethyl)-5-(2-biphenyl)-1,3,4-Thiadiazole (compound 75) possess potent anticonvulsants properties in rat and mice and compared favourably with the standard anticonvulsants drug phenytoin, Phenobarbital and carbamazepine in a number of test situations.

**Fig; Compound 75**

Hatice N.Dogan et.al.⁷⁰ have synthesized a number of compounds and found that compound 76a and 76b showed anticonvulsants activity. They also noticed that these two compounds may be considered promising for the development of new anticonvulsant agents.

**Fig; Compound 76a: R=Ethyl**

Compound 76b: R=*m*-fluorophenyl

Anticancer Activity:-

V.Padmavathi et.al.²⁷ have also found that compound 70d showed maximum cytotoxicity. The other compounds 71d showed appreciable cytotoxicity.

Joanna Matysiak et.al.^{13,72} have synthesized a series of new 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles and evaluated for their antiproliferative activity against the cells of human cancer lines. He found that Derivatives 77 and 78 of different structures prove to be the most active. They exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin.

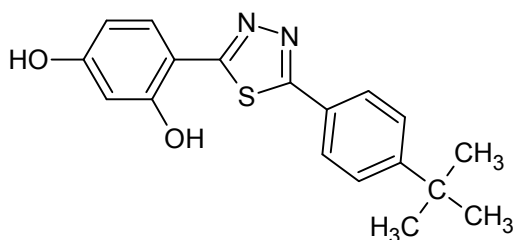


Fig: Compound 77

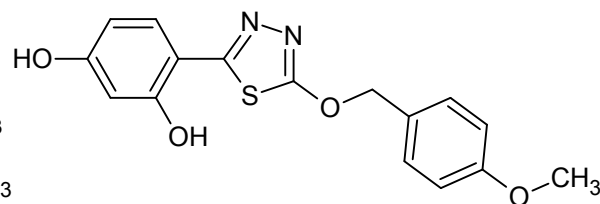
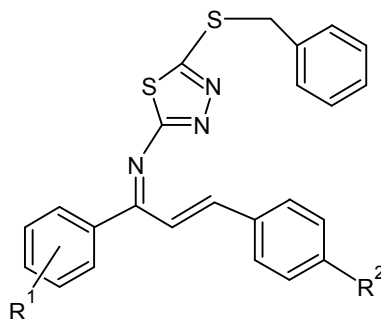


Fig: Compound 78

Antidepressant Activity:-

Bahar Ahmed et.al.⁷¹ have synthesized A number of new imine derivatives of 5-amino-1, 3, 4-thiadiazole-2-thiol, and their anti-depressant activity was tested using imipramine as reference drug. Two compounds namely 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1, 3,4 -thiadiazole (compound 79a) and 5-{[1-(4-chlorophenyl)-3-(4-dimethyl-aminophenyl)-prop-2-en-1-ylidene]amino}-5-benzylthio-1,3,4-thiadiazole (compound 79b) have shown significant anti-depressant activity, which decreased immobility time by 77.99% and 76.26% compared to the standard imipramine (82%). These compounds in the series have passed neurotoxicity tests also.

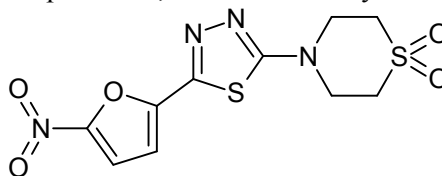


Fig; Compound 79a , R¹= OCH₃ , R²=Cl
Compound 79b , R¹=(CH₃)₂N , R²=Cl

Anti-Helicobacter pylori activity:-

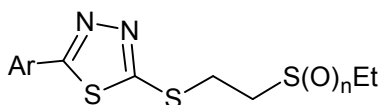
It is now recognized that *Helicobacter pylori*, an S-shaped spiral microaerophilic Gram-negative bacterium first isolated in human gastric mucosa in 1982, is the root cause of gastric and duodenal ulcers, and gastric cancer. Hence, the World Health Organization (WHO) has proposed H. pylori as a class 1 carcinogen in humans.

Alireza Foroumadi et.al.⁷³ have synthesize and evaluated in vitro anti-*Helicobacter pylori* activity of N-[5-(5-nitro-2-heteroaryl)-1, 3, 4-thiadiazol-2-yl] thiomorpholines and some related compounds. They found that nitrofuran analog (compound 80) containing thiomorpholine S, S-dioxide moiety was the most potent compound tested.



Fig; Compound 80

Abbas Shafiee et.al.⁷⁴ have synthesized a series of 5-(nitroaryl)-1,3,4-thiadiazoles bearing certain sulfur containing alkyl side chain similar to pendent residue in tinidazole molecule were synthesized and evaluated against *Helicobacter pylori*. They found that compound 81 containing 2-[2-(ethylsulfonyl)ethylthio]-side chain from nitrothiophene series was the most potent compound tested against clinical isolates of *H. pylori*, however, nitroimidazoles 81b and 82c were found to be more promising compounds because of their respectable anti-*H. pylori* activity.



Fig; Compound 81a, Ar = 5-NO₂-thiophene, n = 2
Compound 82b, Ar = 1-Me-5-NO₂-imidazole n = 2
Compound 83c, Ar = 1-Me-5-NO₂-imidazole n = 0

Conclusion

The synthesis of 1, 3, 4-thiadiazole heterocycles that have been reported to date illustrates different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel chemical derivatives. In general, 1, 3, 4-

thiadiazole derivatives are prepared by appropriate rearrangements, ring opening and substitution reaction. The area of the synthesis of 1, 3, 4-thiadiazole rings continues to grow, and the organic chemistry will provide more and better methods for the synthesis of this interesting heterocycle, allowing the discovery of new drug candidates more active, more specific and safer.

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